Omega-3 Fatty Acids and Ethyl Esters - What Are They?

THOUGHTS TO PONDER

- There are many sources of omega-3 fatty acids, but they vary greatly in their purity and form

Introduction

Omega-3 fatty acids, also referred to as n-3 polyunsaturated fatty acids (n3-PUFA), are marine-derived esters of a combination of EPA and DHA, the 2 primary components of omega-3 fatty acids from fish. Diets high in these oils have long been recognized as beneficial for the reduction of heart disease. Despite this, most individuals in Western countries have a low intake of this nutrient. Dietary supplements have been popular and appear to be beneficial, but their production and labeling do not benefit from US Food and Drug Administration (FDA) regulation, and few well-controlled studies have explored their impact on CV risk.

The American Heart Association (AHA) recommends that healthy adults consume at least 2 servings of fish weekly, particularly those that contain higher levels of omega-3 fatty acids. The AHA further recommends that individuals with known CVD consume approximately 1 g/day of EPA and DHA and that individuals with elevated TG levels may benefit from 2 to 4 g of EPA and DHA daily, since this dose usually results in TG reduction [AHA, Kris-Etherton 2003]. Note, however, that the FDA does not recommend a dose over 3 g/day of EPA and DHA from food and dietary supplements [FDA letter].

BOX 5. What's in a Name?

Fats in food come from a variety of sources, with significant differences in effects on lipid parameters.

Saturated Fats, the "bad" fats, remain soluble at room temperature. These include animal fats and fats used in many processed and refined foods, including baked goods, desserts, and sauces.

Polyunsaturated Fats, the "good" fats, are found in nature and liquefy at room temperature. Available from nuts, plants, and seafood, there are great differences among them in their lipid effects.

Omega Polyunsaturated Fats include:

Omega-6 fatty acids – (contain linolenic acid [LA] and arachidonic acid [AA])
This family of fatty acids has shown some beneficial effects on CVD, but it is not clear what direct effects are exerted on TG levels. The omega-6 family has also been associated with hyperinsulinemia in some studies and a potential for atherogenicity.

Omega-3 fatty acids – (contain EPA, DHA, and alpha-linolenic acid [ALA])
It is the EPA/DHA component of omega-3 fatty acids that is associated with reductions in TG levels. Similar reductions are not seen with ALA-type omega-3 fatty acids.

Omega-3 Acid Ethyl Esters are concentrated forms of fatty acids derived from natural sources through a manufacturing process that increases purity while it removes pollutants and toxins.

Marine-Based Omega-3 Acid Ethyl Esters provide the highest concentration of EPA/DHA from the best natural sources.

Box 5. What's in a Name?

Both EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and they also inhibit the use of other fatty acids in TG synthesis [Omacor® PI]. In addition, there may be other mechanisms by which they may reduce TG levels.

BOX 6. What Do Omega-3 Acid Ethyl Esters Do?

Improve:	*Decrease:*
• Lipid metabolism	• Coagulability
• BP and coronary arterial compliance	• Vascular reactivity
• Endothelial function	• Atherogenecity of VLDL particles

Box 6. What Do Omega-3 Acid Ethyl Esters Do?

Omega-3 Fatty Acids and Cardioprotection

In general, saturated fats elevate LDL-C levels and increase risk for CVD. Polyunsaturated fats in general are a far healthier alternative [Dubnov], but they vary considerably in their relationship to atherosclerosis risk. Polyunsaturated fatty acids are primarily found in fish and plant oils. Omega-3 fatty acids, largely from fish, include EPA and DHA. Omega-6 fatty acids are mainly plant derived and include linolenic acid (LA), gamma-linolenic acid (GLA), and arachidonic acid (AA). Linolenic acid is the major polyunsaturated component of omega-6 fatty acids. In some studies, foods with omega-6 fatty acids still show benefits against CVD and diabetes, and in others omega-6 fatty acids have been linked to hyperinsulinemia and increased atherogenicity [Dubnov]. Data regarding the

effects of omega-6 fatty acids on CVD are inconclusive and warrant further study.

The Importance of Ratios

Two ratios become very significant when considering omega fatty acids and CV risk. The first is the ratio of omega-3 to omega-6 fatty acids. The most beneficial ratio for endothelial function is higher omega-3: omega-6, rather than balanced ratios or higher omega-6 to omega-3. Further study is needed to elucidate and explain these findings, but government reports already recommend that the ratio of omega-6 to omega-3 fatty acids should always be estimated and reported in supplements [Wang]. Omega-6 and omega-3 fatty acids compete for conversion into their active metabolites, and it may be important to achieve a balance in favor of omega-3 fatty acids [Harris].

A second ratio of interest is that of EPA to DHA, the 2 essential fatty acids in the omega-3 family. They are found in the highest concentrations in the oiliest fish types—mackerel, herring, sardines, salmon, and tuna. EPA and DHA are not produced by the fish themselves, but are consumed in their diet in single-celled organisms [Harris]. The natural concentrations of EPA and DHA (combined) in fish oil is approximately 30%. The natural ratio of EPA to DHA is approximately 3:2.

Manufacturing Process

Because large doses of EPA and DHA are needed for antithrombotic and antiatherogenic effects, along with tolerability and convenience issues with consuming large doses, the purity of an EPA or DHA preparation is of clinical importance. The mean concentration of EPA or DHA in dietary supplement forms of omega-3 fatty acids is approximately 30%, although there are significant variations between brands and sometimes even within the same brand. Furthermore, the clinical efficacy of these less pure preparations is poorly understood because most of the reliable prospective cohort studies examined fish intake and not the use of fish-oil dietary supplements [Wang].

The first prescription omega-3 formulation (Omacor®, Reliant Pharmaceuticals, Inc.) provides the highest available concentrations of EPA (465 mg/g) and DHA (375 mg/g). Most importantly, its manufacturing is closely regulated to provide consistent dosing.

Taking a greater number of dietary supplement capsules daily may produce benefits similar to those found with the higher purity FDA-approved formulation, but head-to-head studies comparing supplements with the prescription product have not been conducted, thus the relative clinical efficacy of supplementary fish oil remains unclear. The FDA also does not recommend >3 g daily of dietary omega-3 supplements.

The rigors of processing may eliminate potential adverse effects of pollutants that may be found in a simple extract of fish. The Omacor® omega-3 acid ethyl ester formulation is obtained via a proprietary manufacturing process that is verified to eliminate heavy metals and other environmental pollutants commonly detected in commercially available omega-3 products. However, safety comparisons of dietary supplements with the prescription omega-3 formulation have not yet been conducted in a head-to-head fashion.

Omega-3's From Fish

The traditional source of omega-3 fatty acids is fish, particularly oily fish such as wild salmon and mackerel. In countries such as Japan, where fish is a dietary staple and fish products are a part of many everyday foods, the rate of CVD is among the lowest in the world. But how much fish consumption is required to reduce atherosclerosis, or even to lower TG levels? As Table 5 shows, only high fish intake can provide the recommended 2 to 4 g daily of EPA plus DHA. The amount of omega-3 content from fish is variable. Of note, the US Environmental Protection Agency (EPA) in 2003 issued warnings in 48 states about pollutants in fish and fish oil, such as mercury, dioxin, DDT, and other chemicals [Reuters 2004, EPA 2003]. Both the EPA and the FDA have raised toxicity concerns about consumption of high quantities of fish, especially in pregnant women and children [EPA 2003, FDA & EPA 2004], and the AHA has similar concerns [AHA].

TABLE 5. Amount of Omega-3 Fatty Acid in Various Types of Fish and Seafood		
Type of fish/seafood	Grams omega-3 oil per 3-oz serving	Ounces per day equal 1 g EPA/DHA
Mackerel	0.34 – 1.57	2 – 8.5
Herring (Pacific/Atlantic)	1.71 – 1.81	1.5 – 2
Salmon (Atlantic, farmed)	1.09 – 1.83	1.5 – 2.5
Salmon (Atlantic, wild)	0.9 – 1.56	2 – 3.5
Trout	0.84 – 0.98	3 – 3.5
Tuna (canned)	0.26 – 0.73	4 – 12
Tuna (fresh)	0.96 – 1.70	2 – 3
Shrimp	0.27	11
Cod	0.13	23

Adapted from Harris WS. Cleve Clin J Med. 2004;71:208-221.Source: US Department of Agriculture Nutrient Data Laboratory, February 2004.
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In most Western countries, many people find it difficult to ingest TG-reducing quantities of omega-3 fatty acids, especially EPA and DHA. Estimates on the amount of EPA and DHA that Americans consume vary. One survey reported a mean intake of 0.10 to 0.2 g of EPA plus DHA per day [Kris-Etherton 2000], and the Continuing Survey of Food Intakes by Individuals (1994-1996, 1998) estimates that there is a mean consumption of 0.03 g of EPA and 0.09 g of DHA for adult Americans (aged 19-70 years) [Institute of Medicine]. The AHA recommends EPA/DHA intake of 1 g/day for persons with known heart disease [AHA, Kris-Etherton 2003].

Numerous dietary supplements of omega-3 fatty acids are available in the United States, including: OmegaBrite® (Omegabrite), Natrol® Essential Fatty Acids (Natrol, Inc.), NatureMade® (Pharmavite®, LLC), Spectrum® (Spectrum Organic Products, Inc.) and CVS® brand (CVS/pharmacy). All of these vary in quantities of EPA/DHA, ranging from 264 g/176 g to 360 g/288 g [product labels].

Omacor® (Omega-3 Acid Ethyl Esters)

Omacor® is the first omega-3 acid ethyl ester product approved by the FDA, and has been extensively studied. In the United States, Omacor® has been approved for use as an adjunct to diet to reduce very high (>500 mg/dL) TG levels in adult patients. This indication is based on 2 studies in which therapeutic efficacy was achieved with 4 g/day of the drug. Patients treated with Omacor® had median reductions in TG of −44.9%, reductions in VLDL of −41.7%, and in non-HDL of −13.8%. Moderate increases in LDL-C from the relatively low baseline of 89 mg/dL (median) were also seen. The drug demonstrated a favorable safety profile.

In Europe, Omacor® has been used extensively and is indicated as an adjuvant treatment in secondary prevention after MI in addition to other standard therapy, and for the treatment of hypertriglyceridemia as either monotherapy or in combination with a statin for patients with moderately elevated TG and elevated LDL-C levels. Twelve studies documented its efficacy in various types of hyperlipidemia using Fredrickson and Lees phenotypes [data on file]. Mean reduction in TG across all studies was 25% with 4 g/day, mostly in patients with mixed dyslipidemia with moderately elevated TG levels [Harris, Data on file]. A pooled analysis across several types of hyperlipidemia showed significant TG reductions across all patient types at 4 g/day of omega-3 acid ethyl esters. These studies, however, have not been evaluated by the FDA.

Studies have shown that the lipid benefits of omega-3 fatty acids are maintained over time. The GISSIPrevenzione trial, a large-scale study of patients on the Mediterranean diet who also took Omacor®, showed continued efficacy and tolerability over 3.5 years [GISSI]. Numerous other studies support the safety of the prescription formulation of 1 to 4 capsules daily alone and in combination with statins.

Dietary Supplements vs Prescription Formulations of Omega-3 Fatty Acids

In a letter released in September 2004, the FDA approved the use of a qualified health claim for foods and dietary supplements containing EPA and DHA. It states that dietary or supplemental EPA and DHA intake should not exceed 3 g/day, and encourages manufacturers of dietary supplements not to recommend doses exceeding 2 g/day [FDA letter].

As previously mentioned, omega-3 fatty acids are available as dietary supplements under numerous brand names. The efficacy of these formulations, if titrated to a similar EPA or DHA dosage as that of the prescription-strength formulation, may be approximately the same. It is the dose of isolated EPA or DHA that is believed to produce the clinical benefits of all fish oil preparations [Kaare].

Safety and efficacy data on dietary supplements are largely lacking, and head-to-head studies have not been conducted across brands. Bioavailability of these agents may vary as well, depending on both the active and inactive ingredients used as well as omega-3 to omega-6 ratios. The dosage needed to achieve therapeutic levels with the dietary supplement formulations of fish oil requires the intake of approximately 7 to 15 capsules daily, compared with 3 to 4 pills of the prescription formulation. Furthermore, because weight loss is also an important part of therapy for many patients, especially those with hypertriglyceridemia, additional caloric intake with dietary supplements may also be a consideration.

Summary

The benefits of omega-3 fatty acids have long been recognized in epidemiologic and prospective studies of heart disease. Although available from dietary sources and through dietary supplementation, the majority of the Western population still fails to ingest optimal amounts of omega-3 fatty acids daily. The development of highly purified prescription (and therefore FDA regulated) omega-3 acid ethyl esters provides the opportunity to efficiently and safely deliver optimal doses of EPA and DHA, the fatty acids with the greatest effects on TG. Additionally, the rigorous manufacturing process and careful selection of marine sources may make the daily use of purified omega-3 acid ethyl esters a practical and safe choice as a major source of omega-3 fatty acids.

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